Case of Fatal Sickle Cell Intrahepatic Cholestasis Despite Use of Exchange Transfusion in an African-American Patient

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Sickle cell intrahepatic cholestasis (SCIC) is a rare complication of sickle cell anemia, characterized by marked hyperbilirubinemia and acute hepatic failure with an often fatal course. However, the few reported adult cases that were treated with exchange transfusion had a favorable outcome. We herein describe a 48-year-old African-American man with hemoglobin S/ß thalassemia and previously treated hepatitis C with compensated cirrhosis, who presented with a total bilirubin of 59.7 mg/dL and direct bilirubin of 43.6 mg/dL in the absence of choledocholithiasis. Despite an exchange transfusion and aggressive packed red blood cell transfusions, which successfully decreased the hemoglobin S levels to <15%, he perished from progressive hepatic and renal failure. Autopsy demonstrated extensive intrahepatocellular and intracanalicular cholestasis in a background of cirrhosis. Our case suggests that poor prognostic factors for adult SCIC patients treated with exchange transfusion may include older age and underlying hepatic disease.

Key words: sickle cell disease ■ sickle cell intrahepatic cholestasis ■ exchange transfusion ■ hepatitis C ■ cirrhosis

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INTRODUCTION

Hepatobiliary complications of sickle cell disease encompass many insults that range from benign liver function abnormalities to acute hepatic failure.[1] A rare entity named sickle cell intrahepatic cholestasis (SCIC) has been reported in <14 adults with sickle cell anemia.[1-15] This clinical syndrome is characterized by marked hyperbilirubinemia with acute hepatic failure and is frequently accompanied by renal dysfunction.[1-3,6] SCIC has been described in sickle cell patients who are homozygous for hemoglobin S (HbS), as well as in those who are heterozygous for HbS and ß thalassemia.[1,3-6,10]

Historically, SCIC proved fatal despite aggressive supportive care.[2,7-9] However, since the advent of exchange transfusion, attempts have been made to lower the HbS fraction in patients with SCIC in order to minimize intrahepatic sickling. The four previously reported adults (ages 21–37) who had received exchange transfusions for SCIC survived.[3-6]

We present the case of a middle-aged man with HbS/ß thalassemia and previously treated hepatitis C with compensated cirrhosis, who presented with SCIC. Despite an exchange transfusion and aggressive packed red blood cell (PRBC) transfusions, which decreased the HbS levels to <15%, he perished from progressive hepatic and renal failure.

CASE REPORT

The patient was a 48-year-old African-American man with HbS/ß thalassemia. Hemoglobin electrophoresis at age 29 showed HbS 91.3%, HbF 2.6%, HbA2 6% and HbA 0%. The patient had a cholecystectomy at age 35 due to gallstone disease, and an abnormal liver was noted during the operation. Biopsy demonstrated cirrhosis, with mild chronic inflammation of fibrous septae and focal iron deposition within Kupffer cells and hepatocytes. Hepatitis C was diagnosed by serology; genotype and viral load assays were not commercially available. Apart from blood transfusions, he had no other known risk factor for hepatitis C. Interferon-α (3 million units three times a week) was started at age 36. After two years of therapy, hepatitis C viral load was undetectable. He had no evidence of portal hypertension or clinical manifestations of cirrhosis. Interferon was continued since the patient reported a decrease in the frequency of painful crises with this therapy. HIV antibody test was negative at age 44. His baseline total bilirubin was below 8 mg/dL for the previous 10 years.

The patient presented to medical care with abdominal discomfort, nausea, vomiting and jaundice for three

weeks. On review of systems, he denied fevers, chills, chest pain, diarrhea and melena. Physical exam demonstrated jaundice as well as a distended abdomen with hepatomegaly and ascites but no asterixis. Laboratory evaluation was notable for a markedly elevated total bilirubin of 59.7 mg/dL (normal 0–1.5 mg/dL) with a direct bilirubin of 43.6 mg/dL. In addition, white blood cell count was 18,000/μL, Hb 6.7 g/dL, hematocrit (Hct) 20.7%, platelet count 225,000/μL, mean corpuscular volume 78 fL, alanine aminotransferase (ALT) 85 U/L, aspartate aminotransferase (AST) 190 U/L, alkaline phosphatase 513 U/L, prothrombin time (PT) 20.1 seconds (normal 11.6–13.6 seconds), INR 2.6, partial thromboplastin time (PTT) 100.2 seconds (normal 22.0–35.0 seconds), and creatinine 3.3 mg/dL (normal 0.5–1.2 mg/dL). Hepatitis A and B serologies were negative. Hepatitis C viral load showed no detectable virus (<600 IU/ml of HCV-RNA by RT-PCR).

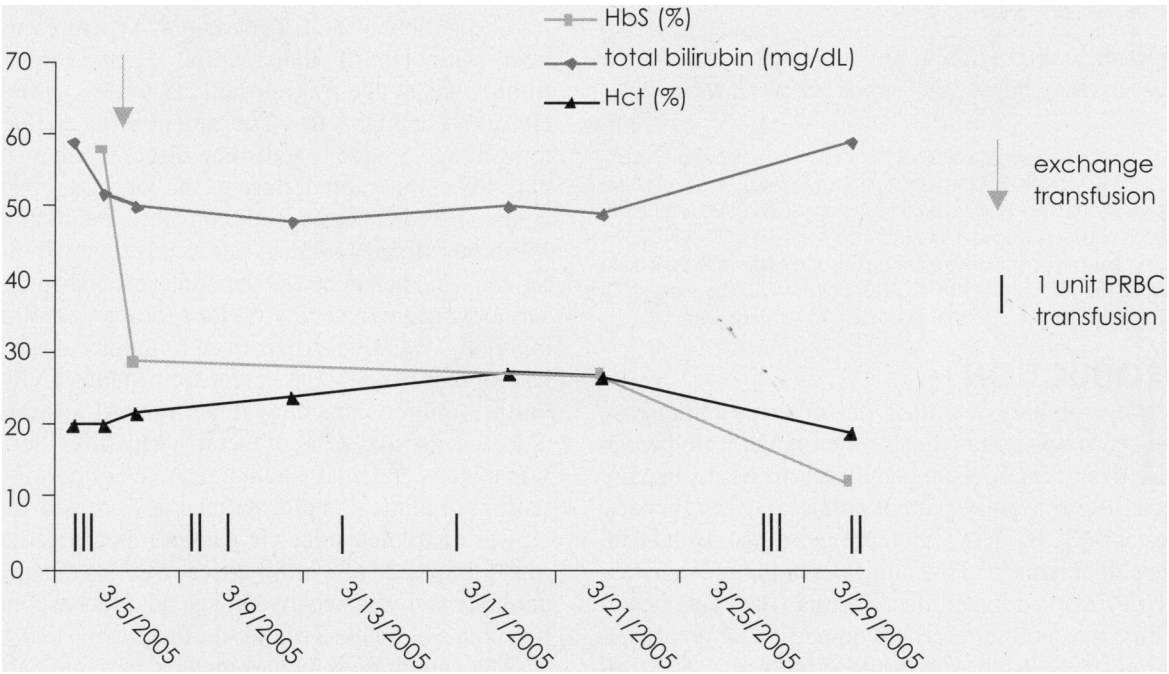
Ultrasound demonstrated patent hepatic vessels and no evidence of choledocholithiasis. Abdominal computed tomography confirmed hepatomegaly and ascites as well as hepatic nodularity. Peripheral blood smear was notable for sickle cells, target cells, many nucleated red blood cells and Howell-Jolly bodies. Cultures from blood, urine and peritoneal fluid were negative.

Initial management consisted of intravenous saline, vitamin K, PRBCs and fresh frozen plasma. He was treated empirically with broad-spectrum antibiotics. Exchange transfusion was initiated within 12 hours of admission due to his multiorgan failure, particularly hepatic dysfunction. Five units of PRBCs were exchanged in one session. Pre- and postexchange transfusion hemoglobin electrophoresis demonstrated a decline in hemoglobin S from 58% to <15% (Figure 1). Despite continued support with fresh frozen plasma and PRBCs, his total bilirubin remained constant around 50 mg/dL. The presumptive clinical diagnosis of SCIC was made, and after initial exchange transfusion therapy, his HbS level was maintained at <25%, and Hct was maintained around 22% with subsequent PRBCs.

Despite an initial clinical improvement with the lowered HbS level, his condition continued to deteriorate. He received aggressive supportive care in the intensive care unit with mechanical ventilation. Both coagulopathy and renal dysfunction persisted, and 20 days after admission his PT was 18.5 seconds, PTT 150 seconds and creatinine 2.5 mg/dL. Due to unresponsive cholestasis, a trial of ursodeoxycholic acid was attempted without benefit to the bilirubin levels. Twenty-six days after his initial admission, the patient succumbed to multiorgan failure. The day prior to his death, the HbS level was 12%.

Autopsy was notable for extensive intrahepatocellular and intracanalicular cholestasis in a background of cirrhosis, and also peripheral hemosiderin deposition consistent with secondary hemochromatosis (Figure 2). There were no thrombi or prominent ischemic changes within the liver parenchyma. Brain dissection showed

Figure 1. Graphic description of hemoglobin S (HbS) levels, total bilirubin and hematocrit (Hct) during inpatient course. Exchange transfusion (arrow corresponds to 5 units of PRBCs that were exchanged in one session), and PRBC transfusions are indicated.



type-2 astrocytes of Alzheimer's, consistent with hepatic encephalopathy.

DISCUSSION

The first comprehensive review of abnormalities within the hepatobiliary tract in patients with sickle cell disease was published in 1977. Eighty-eight cases were reviewed, and five specific syndromes identified.[2] These included viral hepatitis, hepatic crisis, cirrhosis, cholelithiasis with cholecystitis and intrahepatic cholestasis or SCIC.[2] A more contemporary review of sickle cell hepatopathy added new entities such as multitransfusion liver disease and chronic hepatitis B and C infections.[1]

SCIC is a rare but feared morbid complication of sickle cell disease.[1,2,6] The etiology remains unknown, but widespread sickling within liver sinusoids has been postulated.[1,2] The pathophysiology of SCIC is poorly understood, but hepatic sinusoid sickling is thought to cause vascular stasis with subsequent ballooning of hepatocytes, which leads to intracanalicular cholestasis.[1-3,6] Patients with SCIC experience right upper quadrant pain, progressive hepatomegaly, coagulopathy with hemorrhage, and extreme hyperbilirubinemia with total bilirubin levels that reach up to 200 mg/dL.[1,2,4] In most reported cases, the degree of transaminitis is modest (ALT and AST <3 times normal levels) in contrast to the markedly elevated total and conjugated bilirubin.[1] Renal impairment commonly follows liver dysfunction.[1,2]

Liver biopsy and autopsy specimens from afflicted patients generally show dilated intrahepatic canaliculus.[2] Sickle cell thrombi, sinusoidal engorgement, scattered bile stained microinfarcts and Kupffer cell hypertrophy have also been reported.[2-4,8] However, a liver biopsy is not without risks in the diagnostic work-up of acute sickle cell hepatopathy. A report from England showed a 28% incidence of death complicating liver biopsies in 14 patients with sickle cell disease and acute

Figure 2. Autopsy and liver pathology. A: Hepatomegaly (liver weight: 2,200 g) with diffuse micronodular pattern. B: Trichome stain (20x) showed bridging fibrosis (stage 4) and disruption of liver architecture consistent with cirrhosis. C: Picture taken at the center of the nodules showing extensive intrahepatocellular and intracanalicular cholestasis (hematoxylin and eosin 40x). D: Iron stain (20x) showed intense peripheral and scattered intrahepatic hemosiderin deposition, consistent with secondary hemochromatosis.

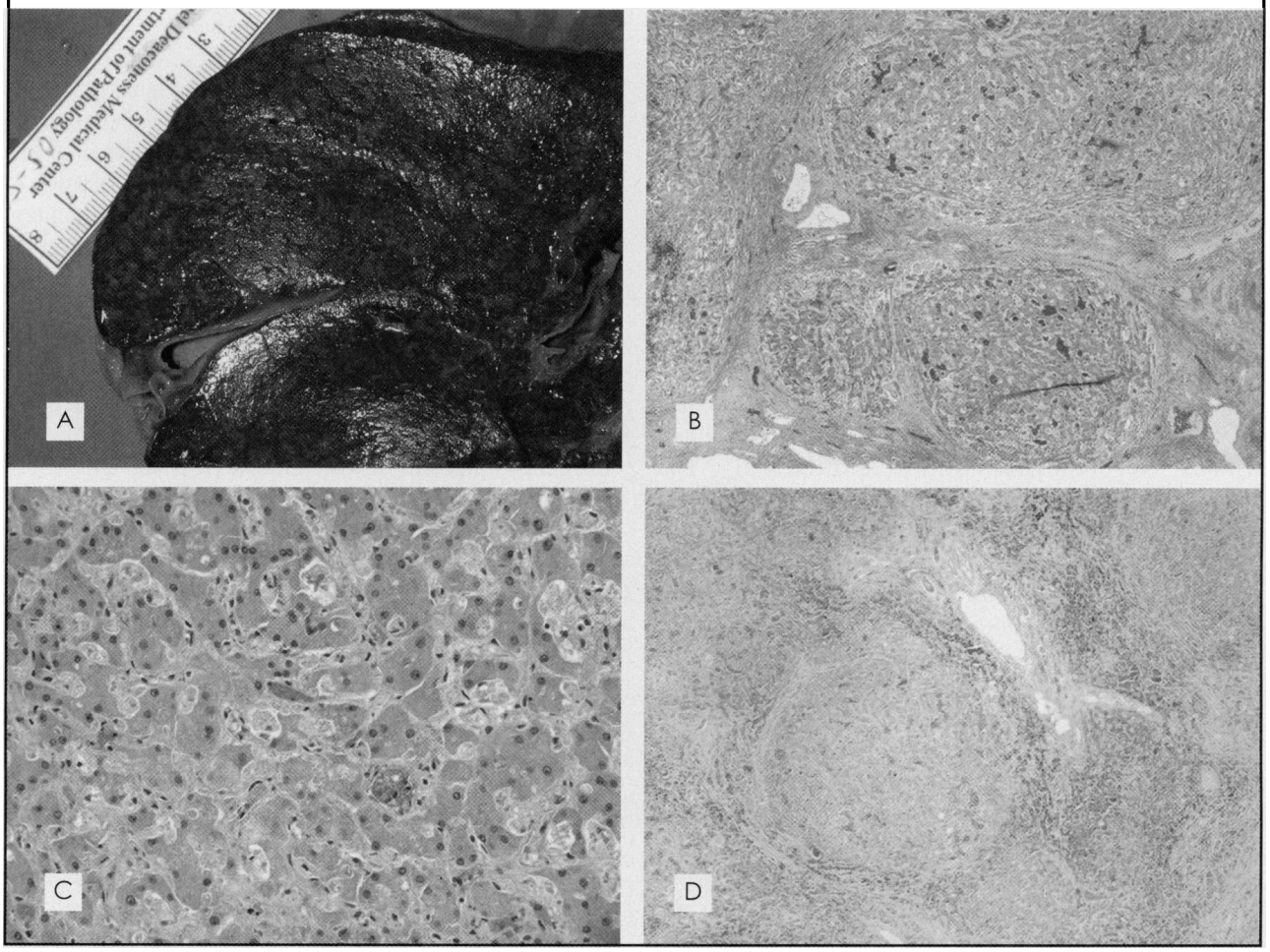


Table 1. Clinical-laboratorial characteristics and outcome of patients over 18 years of age with SCIC

Year of Publication	Age (Years)/Type of of Sickle Cell Syndrome	Total Bilirubin (mg/dL)	Prothrombin Time (Seconds)	Exchange Transfusion of PRBCs	Outcome
1964[7]	24/HbSS	100	-	no	died
1965[8]	23/HbSS	81	-	no	died
1965[8]	22/HbSS	89	-	no	died
1965[8]	20/HbSS	61	-	no	died
1977[2]	33/HbSS	112	53	no	died
1977[2]	35/HbSS	64	-	no	died
1977[2]	23/HbSS	45	-	no	died
1977[2]	44/HbSS	98	47	no	died
1980[3]	21/HbSS	146	29	yes	survived
1986[13]	35/HbSS	75	23	no	survived
1995[4]	29/HbSS	106	35	yes	survived
1996[10]	36/HbS–ß thalassemia	47	32	no	survived
2002[6]	37/HbSS	61	17	yes	survived
2002[5]	22/HbS–ß thalassemia	55	-	yes	survived
2006 (current case)	48/HbS–ß thalassemia	60	20	yes	died

SCIC: sickle cell intrahepatic cholestasis; HbSS: homogyzous for hemoglobin S; HbS: ß thalassemia: compound heterozygous for hemoglobin S and ß thalassemia; PRBCs: packed red blood cells

hepatic disease. The authors concluded that within that clinical setting percutaneous liver biopsy is contraindicated.[16] The diagnosis of SCIC is usually established by the characteristic clinical and laboratory findings in the absence of choledocholithiasis impacting within the biliary tract.[1,6]

Fewer than 32 cases of SCIC have been reported.[1-15] The incidence seems to be greater in the pediatric than adult population. Although the mortality in children can be as much as 30%, their clinical course can also be mild and sometimes self-limiting.[1,11-15] The management and outcomes of children have been reviewed elsewhere.[1,6,14]

We will focus our discussion on the adult population. Only 14 patients (Table 1) >18 years of age have been reported with SCIC.[1-10,13] The first cases identified in the 1960s and '70s proved to be almost invariably fatal, despite use of PRBCs and supportive measures.[2,7-9] Of the four cases reported after 1980 of adult SCIC treated with exchange transfusion, all were successful.[3-6] The first successful use of exchange transfusion led to a decrease in the HbS level to 30% associated with a decrease in bilirubin from 146- to 16 mg/dL and with survival.[3] Similar dramatic improvements have been described in three additional adults treated with exchange transfusion, though in some the clinical course was more protracted.[4-6] Two other reported adult cases of SCIC were successfully treated with only PRBCs and fresh frozen plasma.[10,13]

We were unable to find a report in an adult patient where exchange transfusion did not result in resolution of the hyperbilirubinemia, hepatic dysfunction and multiorgan failure. While reporting bias may limit the publication of unsuccessful cases, our patient highlights the fact that SCIC continues to be a severe and potentially fatal complication for adults with sickle cell disease.

Two characteristics of our patient—prior hepatic injury from hepatitis C/cirrhosis and older age—may have contributed to the observed poorer outcome when compared to that expected from the SCIC literature. However, his undetectable hepatitis-C viral load, modest hyperbilirubinemia, and complete absence of signs and symptoms of liver disease prior to his acute presentation go against hepatitis-C-induced hepatic failure as the sole cause of his refractoriness. Another consideration is that at age 48, our case is the oldest reported in the literature. In the only other SCIC patient >30 years old treated with exchange transfusion, it took almost a month to see clinical improvement.[6]

In conclusion, SCIC is a rare hepatobiliary complication of sickle cell disease that can be highly lethal. Despite the favorable outcomes of the adult cases in which prompt clinical diagnosis was made and exchange transfusions with a target HbS <20–30% were performed, our case illustrates that such positive results may not always be achievable. Based on our case report, a worse response to exchange transfusion in SCIC may be expected in older patients and in those with prior hepatic disease, such as hepatitis C and cirrhosis.

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